REMARKS

Claims 1-63 were pending. Claims 1, 19, and 56 have been amended. Therefore, claims 1-63 are pending. No new matter has been added.

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application.

Provisional Rejection of Claims 1-63 under Judicially Created Doctrine of Double Patenting

Claims 1-63 are provisionally rejected under the judicially created doctrine of double patenting over claims 1 and 3-61 of copending application, U.S.S.N. 09/298,395. Applicants note that U.S. Application No. 09/298,395 is pending and, therefore, the double patenting rejections are provisional. Applicants will timely file, if necessary, a terminal disclaimer in compliance with 37 C.F.R. §1.321 upon the issuance of U.S. Application No. 09/298,395.

Rejection of Claims 1-43 under 35 U.S.C. § 112, first paragraph

Claims 1-43 are rejected under 35 U.S.C. § 112, first paragraph, because the Examiner alleged that "the specification while being enabling for treatment of specific nervous system disease, comprising the administration of creatine compounds does not provide enablement for the administration of the creatine compound, wherein the administration of the creatine compounds results in (a) elimination of all symptoms...(b) preventing the occurrence of any or all types of nervous system disease within in a subject." The Examiner noted that "this rejection may be overcome by deleting the word 'preventing' from the claims and limiting the claims to 'treatment' type language."

It is respectfully submitted that this rejection no longer pertains to the claims as currently amended. Therefore, Applicants respectfully request that this rejection of claims 1-43 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of Claims 1-24 under 35 U.S.C. § 102(b)

Claims 1-24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hagenfeldt *et al.* (Muscle and Nerve, Oct. 17, 1994, (10), 1236-7) (hereinafter

"Hagenfeldt *et al.*"). According to the Examiner, "Hagenfeldt *et al.* discloses the use of creatine in a therapeutic use for the treatment of a nervous system disease in human patients."

Claims 1-18 are directed to methods for of increasing ATP production in the brain of a subject, by administering to the subject an effective amount of a creatine compound and an ATP enhancing agent. Claims 19-24 are directed to methods of treating nervous system disorders, by administering to a subject an effective amount of a creatine compound and a neuroprotective agent.

Hagenfeldt *et al.* discusses treating one MELAS patient with creatine supplementation. MELAS is characterized as a mitochondrial myopathy, characterized by seizures, episodes of transient or persistent neurologic dysfunction, and ragged-red fibers in muscle biopsies.

Hagenfeldt *et al.* neither teaches nor suggests treating a subject by administering a creatine compound in combination with a neuroprotective agent, as claimed by Applicants. Furthermore, Hagenfeldt *et al.* neither teaches nor suggests methods of increasing ATP production in the brain. Therefore, Applicants respectfully request that this rejection of claims 1-24 under 35 U.S.C. § 102 (b) be withdrawn.

Rejection of Claims 1-43 under 35 U.S.C. § 103(a)

Claims 1-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hagenfeldt *et al.*, Applicants' admission in the present specification, and Schultheiss *et al.* (*J. Neurochemistry*, June, 1990, 54(6), 1858-63) (hereinafter "Schultheiss *et al.*").

As discussed above, claims 1-18 are directed to methods for of increasing ATP production in the brain of a subject, by administering to the subject an effective amount of a creatine compound and an ATP enhancing agent. Claims 19-33 are directed to methods of treating nervous system disorders, by administering to a subject an effective amount of a creatine compound and a neuroprotective agent. Claims 34-39 are directed to methods of protecting the nervous system of a subject against oxidative damage, by administering to a subject an effective amount of a creatine compound and a neuroprotective agent. Claims 40-43 are directed to methods of treating a subject suffering from a nervous system disorder, by administering to the subject a creatine kinase modulating compound which enhances ATP production and a neuroprotective agent.

As discussed above, Hagenfeldt *et al.* discusses the results of a clinical experiment of administering creatine to a MELAS patient. It was found that the patient

had improved muscle function and fewer headaches after three months of creatine administration. Hagenfeldt *et al.* does not teach or suggest methods involving the administration of creatine in combination with a neuroprotective agent. Furthermore, Hagenfeldt *et al.* does not teach or suggest methods comprising the administration of a creatine kinase modulating compound, as claimed by Applicants.

The Applicants' specification is not available as prior art under 35 U.S.C. § 103(a).

Schultheiss *et al.* is directed to a study of the effects of creatine on the synthesis and release of γ-[^{3}H]-aminobutyric acid (GABA) in rat brain slices. Schultheiss found that creatine affects GABA synthesis in rat brain slices. On page 1863, Schultheiss *et al.* teach away from Applicants' invention by stating that "[i]n view of the high concentrations of creatine necessary to obtain these effects, these findings do not have pathophysiological implications."

Schultheiss *et al.* fails to overcome the deficiencies of Hagenfeldt *et al.* Like Hagenfeldt *et al.*, Schultheiss *et al.* also fails to teach or suggest methods using creatine or a creatine kinase modulator in combination with a neuroprotective agent. Therefore, Applicant respectfully requests that this rejection of claims 1-43 under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claims 44-61 under 35 U.S.C. § 102(b)

Claims 44-61 are rejected under 35 U.S.C. § 102(b) as being anticipated by Boehm *et al.* (*Biochem et Biophysica Acta*, 1274 (1996) 119-128) (hereinafter "Boehm *et al.*"). The Examiner alleged that "Boehm *et al.* teach creati[n]e analogues as recited in the claims."

Claims 44-46 are directed to methods of treating a subject suffering from a nervous system disorder, by administering to the subject a creatine kinase modulating compound which enhances ATP production and a neuroprotective agent. Claims 47-55 are directed to methods for protecting the nervous system against nervous system disease states, by administering to a subject a dietary food supplement containing a creatine compound and a neuroprotective agent. Claims 56-61 are directed to methods for treating memory impairment in a subject, by administering to the subject an effective amount of a creatine kinase modulating compound and a neuroprotective agent.

Boehm *et al.* studied several creatine analogs as indicated by the Examiner. Boehm *et al.* studied these analogues *in vitro* using mitochondria and skinned fibers. However, Boehm *et al.* does not teach or suggest methods for treating subjects suffering

from nervous system disorders, methods for protecting the nervous system, nor methods of treating memory impairment.

Therefore, Applicants respectfully requests that this rejection of claims 44-61 under 35 U.S.C. § 102 (b) be withdrawn.

Rejection of Claims 44-61 under 35 U.S.C. § 103 (a)

Claims 44-61 are rejected under 35 U.S.C. § 103 (a) as being anticipated by Boehm *et al.* The Examiner stated that since "Boehm *et al.* teach creati[n]e analogues as recited in the claims...one of ordinary skill would similar (*sic*) other closely structurally related compounds to have similar properties."

As discussed above, claims 44-46 are directed to methods of treating a subject suffering from a nervous system disorder, by administering to the subject a creatine kinase modulating compound which enhances ATP production and a neuroprotective agent. Claims 47-55 are directed to methods for protecting the nervous system against nervous system disease states, by administering to a subject a dietary food supplement containing a creatine compound and a neuroprotective agent. Claims 56-61 are directed to methods for treating memory impairment in a subject, by administering to the subject an effective amount of a creatine kinase modulating compound and a neuroprotective agent.

As mentioned above, Boehm *et al.* used several creatine analogs *in vitro* to test their effect of skinned fibers and heart mitochondria. However, Boehm *et al.* does not teach or suggest methods for treating subjects suffering from nervous system disorders, methods for protecting the nervous system, nor methods of treating memory impairment. Therefore, the presently claimed methods of treating subjects, by administering at least a creatine compound and a neuroprotective agent or an ATP enhancing agent would not have been obvious to the ordinarily skilled artisan.

Therefore, Applicants respectfully request that this rejection of claims 44-61 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSIONS

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

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Marked Up Version of Claims to Show Changes Made

1. [Amended] A method of increasting ATP production in the brain of a subject, comprising administering to saida subject an effective amount of a creatine compound and an ATP enhancing agent, such that the ATP production in the brain is increased.

19. [Amended] A method of treapreventing a nervous system disorders, comprising administering to a subject an effective amount of a creatine compounds and a neuroprotective agent, such that said nervous system disorders isare treaprevented.

56. [Amended] A method for treating memory impairment in a subject, comprising administering to said subject an effective amount of a creatine kinase modulating compound and a neuroprotective agent, such that said memory impairment is treated in said subject.